ESTROGEL - estradiol gel, metered
ASCEND Therapeutics, Inc.

Rx only
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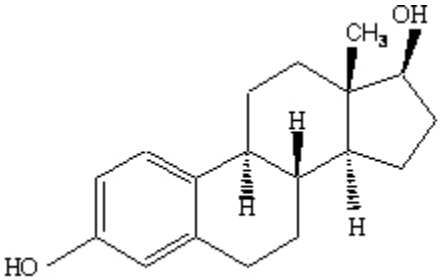
WARNINGS

ENDOMETRIAL CANCER
Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. (See WARNINGS, Malignant neoplasms, *Endometrial cancer*.)
CARDIOVASCULAR AND OTHER RISKS
Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See CLINICAL STUDIES and WARNINGS, Cardiovascular disorders and Dementia.)
The Women's Health Initiative (WHI) estrogen alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50-79 years of age) during 6.8 and 7.1 years, respectively, of treatment with daily oral conjugated estrogens (CE 0.625 mg), relative to placebo. (See CLINICAL STUDIES and WARNINGS, Cardiovascular disorders.)
The estrogen plus progestin WHI substudy reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and DVT in postmenopausal women (50-79 years of age) during 5.6 years of treatment with daily oral CE 0.625 mg combined with medroxyprogesterone acetate (MPA 2.5 mg), relative to placebo. (See CLINICAL STUDIES and WARNINGS, Cardiovascular disorders and Malignant neoplasms, *Breast cancer*.)
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE 0.625 mg alone and during 4 years of treatment with daily CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL STUDIES and WARNINGS, Dementia, and PRECAUTIONS, Geriatric Use.)
In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

EstroGel® (estradiol gel) contains 0.06% estradiol in an absorptive hydroalcoholic gel base formulated to provide a controlled release of the active ingredient. It is a clear, colorless gel, which is odorless when dry. The gel is applied over a large area (750 cm^2) of the skin in a thin layer. The recommended area of application is the arm, from wrist to shoulder. An EstroGel unit dose of 1.25 g contains 0.75 mg of estradiol.
Estradiol is a white crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.39. The structural formula is:



The active component of the transdermal gel is estradiol. The remaining components of the gel (purified water, alcohol, triethanolamine and carbomer 934P) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

EstroGel provides systemic estrogen replacement therapy by releasing estradiol, the major estrogenic hormone secreted by the human ovary.
Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.
Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.
Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics
A. Absorption
Estradiol is transported across intact skin and into the systemic circulation by a passive diffusion process. The rate of diffusion across the stratum corneum is the rate-limiting factor. When EstroGel is applied to the skin, it dries in 2 to 5 minutes.
EstroGel 1.25 g was administered to 24 postmenopausal women once daily on the posterior surface of 1 arm from wrist to shoulder for 14 consecutive days. Mean maximal serum concentrations of estradiol and estrone on Day 14 were 46.4 pg/mL and 64.2 pg/mL, respectively. The time-averaged serum estradiol and estrone concentrations over the 24-hour dose interval after administration of 1.25 g EstroGel on Day 14 are 28.3 pg/mL and 48.6 pg/mL, respectively. Mean concentration-time profiles for unadjusted estradiol and estrone on Day 14 are shown in Figure 1.

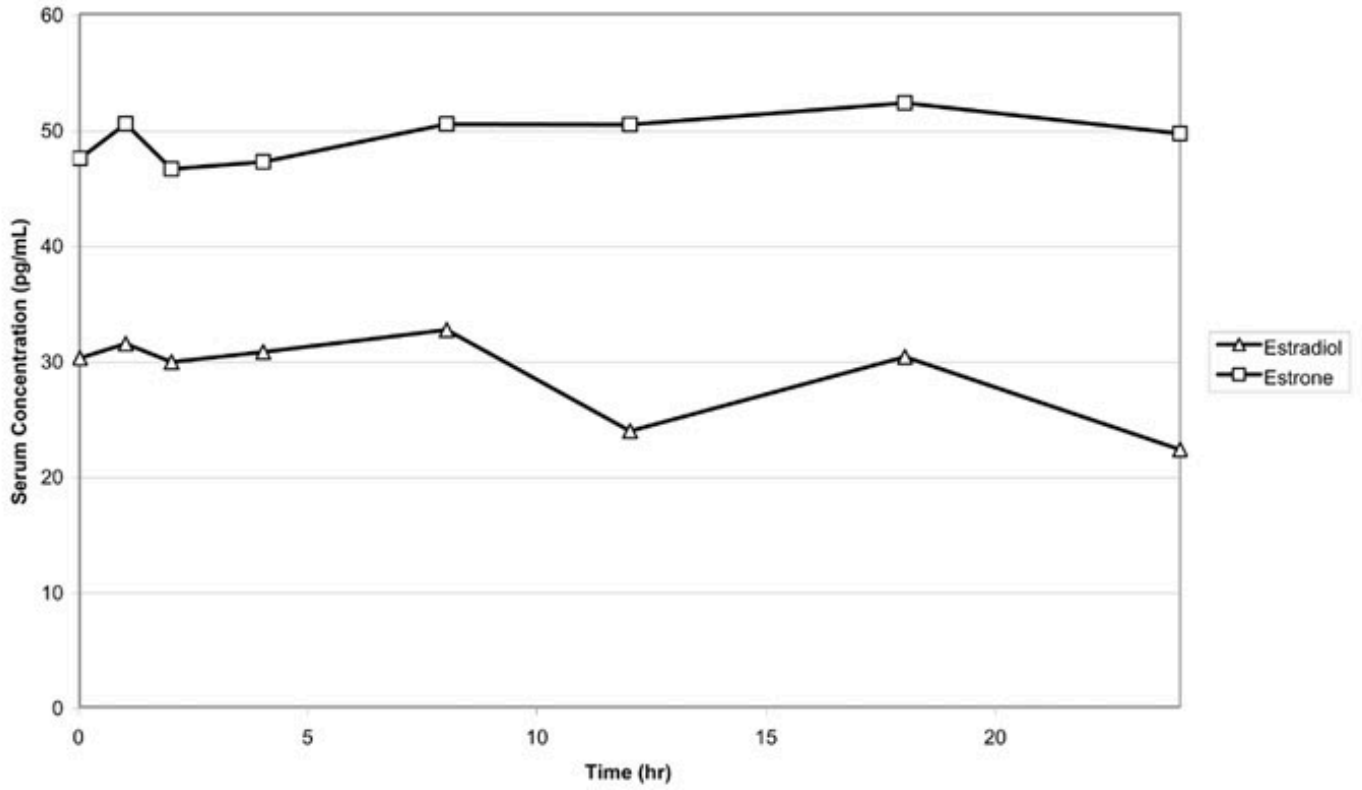


FIGURE 1 Mean Serum Concentration-time Profiles for Unadjusted Estradiol and Estrone After Multiple-dose Applications of 1.25 g EstroGel for 14 Days

The serum concentrations of estradiol following 2.5-g EstroGel applications (1.25 g on each arm from wrist to shoulder) appeared to reach steady state after the third daily application.
B. Distribution
The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in blood largely bound to sex hormone-binding globulin (SHBG) and albumin.
C. Metabolism
Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly

to estrone, and both can be converted to estriol, the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Although the clinical significance has not been determined, estradiol from EstroGel does not go through first-pass liver metabolism.

D. Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

The apparent terminal exponential half-life for estradiol was about 36 hours following administration of 1.25 g EstroGel.

E. Special populations

EstroGel has been studied only in postmenopausal women. No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

F. Drug interactions

No formal drug interaction studies have been conducted for EstroGel.

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of estrogen and may result in side effects.

G. Potential for estradiol transfer and effects of washing

The effect of estradiol transfer was evaluated in 24 healthy postmenopausal women who topically applied 1.25 g of EstroGel once daily on the posterior surface of 1 arm from wrist to shoulder for a period of 14 consecutive days. On each day, 1 hour after gel application, a cohort of 24 non-dosed healthy postmenopausal females directly contacted the dosed cohort at the site of gel application for 15 minutes. No change in endogenous mean serum concentrations of estradiol was observed in the non-dosed cohort after direct skin-to-skin contact with subjects administered EstroGel.

The effect of application site washing on the serum concentrations of estradiol was determined in 24 healthy postmenopausal females who applied 1.25 g of EstroGel once daily for 14 consecutive days. Site washing 1 hour after the application resulted in a 22% mean decrease in average 24-hour serum concentrations of estradiol.

CLINICAL STUDIES

Effects on vasomotor symptoms

In a placebo-controlled study, 145 postmenopausal women between 29 and 67 years of age (81.4% were White) were randomly assigned to receive 1.25 g of EstroGel (containing 0.75 mg of estradiol) or placebo gel for 12 weeks. Efficacy was assessed at 4 and 12 weeks of treatment. A statistically significant reduction in the frequency and severity of moderate to severe hot flushes was shown at Weeks 4 and 12. (See Table 1)

TABLE 1 Mean Change from Baseline in the Number and Severity of Hot Flushes per Day, ITT Population, LOCF

	Number of Hot Flushes/Day (Moderate to Severe)		**Severity Score/Day (Mild, Moderate, Severe)**	
	Placebo n=73	EstroGel 1.25 g n=72	Placebo n=73	EstroGel 1.25 g n=72
Baseline				
Mean (SD)	11.01 (5.66)	10.33 (3.07)	2.30 (0.24)	2.36 (0.29)
Week 4*	5.95 (5.17)		2.00 (0.63)	
Mean (SD)	-5.06 (4.91)	4.43 (4.13)	-0.31 (0.62)	1.73 (0.73)
Mean change from baseline (SD)		-5.91 (3.68)		-0.63 (0.71)
Diff. vs placebo		0.85		0.32
P value†		0.019‡		0.005‡
Week 12*	5.17 (6.52)		1.76 (0.84)	
Mean (SD)	-5.84 (4.52)	2.79 (3.70)	-0.54 (0.84)	1.33 (0.97)
Mean change from baseline (SD)		-7.55 (3.52)		-1.03 (0.94)
Diff. vs placebo		1.71		0.49
P value†		0.043‡		<0.001‡

*****Primary timepoint

†*P* values from Elteren's nonparametric test.

‡Statistically significantly different from placebo.

Effects on vulvar and vaginal atrophy

Results of the vaginal wall cytology showed a significant ($P \leq 0.001$) increase from baseline in the percent of superficial epithelial cells at Week 12 for 1.25 g EstroGel. In contrast, no significant change from baseline was observed in the placebo group.

Transdermal effects

In 2 controlled clinical trials, application site reactions were reported by 0.6% of patients who received 1.25 g of EstroGel. Other skin reactions, such as pruritus and rash, were also noted. (See Table 4.)

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of either the use of daily oral conjugated estrogens (CE 0.625 mg) alone or in combination with medroxyprogesterone acetate (MPA 2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction (MI), silent MI, and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the CE/MPA substudy), colorectal cancer, hip fracture, or death due to other causes. These studies did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The estrogen alone substudy was stopped early because an increased risk of stroke was observed and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Results of the estrogen alone substudy, which included 10,739 women (average age of 63 years, range 50-79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other), after an average follow-up of 6.8 years are presented in Table 2.

TABLE 2 Relative and Absolute Risk Seen in the Estrogen Alone Substudy of WHI

Event	Relative Risk CE vs Placebo (95% nCI*)	Placebo n = 5,429	CE n = 5,310
		Absolute Risk per 10,000 Women-Years	
CHD events†	0.95 (0.79-1.16)	56	53
Nonfatal MI†	*0.91 (0.73-1.14)*	*43*	*40*
CHD death†	*1.01 (0.71-1.43)*	*16*	*16*
Stroke†	1.37 (1.09 -1.73)	33	45
Ischemic†	1.55 (1.19-2.01)	25	38
Deep vein thrombosis†‡	1.47 (1.06-2.06)	15	23
Pulmonary embolism†	1.37 (0.90-2.07)	10	14
Invasive breast cancer†	0.80 (0.62-1.04)	34	28
Colorectal cancer§	1.08 (0.75-1.55)	16	17
Hip fracture§	0.61 (0.41-0.91)	17	11
Vertebral fractures§‡	0.62 (0.42-0.93)	17	11
Total fractures§‡	0.70 (0.63-0.79)	195	139
Death due to other causes§¶	1.08 (0.88-1.32)	50	53
Overall Mortality§‡	1.04 (0.88-1.22)	78	81
Global index§#	1.01 (0.91-1.12)	190	192

*****Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

†Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

‡Not included in Global Index.

§Results are based on an average follow-up of 6.8 years.

¶All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.

#A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 6 fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant 2 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Final centrally adjudicated results for CHD events and centrally adjudicated results for invasive breast cancer incidence from the estrogen alone substudy, after an average follow-up of 7.1 years, reported no overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE alone compared with placebo (see Table 2).
The estrogen plus progestin substudy was also stopped early. According to the predefined stopping rule, after an average follow-up of 5.2 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years (relative risk [RR] 1.15, 95% nCI, 1.03-1.28).
For those outcomes included in the "global index," that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 6 more CHD events, 7 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 7 fewer colorectal cancers and 5 fewer hip fractures. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)
Results of the estrogen plus progestin substudy, which included 16,608 women (average age of 63 years, range 50-79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other), are presented in Table 3.

TABLE 3 Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years*

Event	Relative Risk CE/MPA vs Placebo at 5.6 Years (95% nCI†)	Placebo n = 8,102	CE/MPA n = 8,506
		Absolute Risk per 10,000 Women-Years	
CHD events	1.24 (1.00-1.54)	33	39
Non-fatal MI	*1.28 (1.00-1.63)*	*25*	*31*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All strokes	1.31 (1.02-1.68)	24	31
Ischemic stroke	*1.44 (1.09-1.90)*	*18*	*26*
Deep vein thrombosis	1.95 (1.43-2.67)	13	26
Pulmonary embolism	2.13 (1.45-3.11)	8	18
Invasive breast cancer‡	1.24 (1.01-1.54)	33	41
Invasive colorectal cancer	0.56 (0.38-0.81)	16	9
Endometrial cancer	0.81 (0.48-1.36)	7	6
Cervical cancer	1.44 (0.47-4.42)	1	2
Hip fracture	0.67 (0.47-0.96)	16	11
Vertebral fractures	0.65 (0.46-0.92)	17	11
Lower arm/wrist fractures	0.71 (0.59-0.85)	62	44
Total fractures	0.76 (0.69-0.83)	199	152

*****Results are based on centrally adjudicated data. Mortality data was not part of the adjudicated data: however, data at 5.2 years of follow-up showed no difference between the groups in terms of all-cause mortality (RR 0.98, 95% nCI, 0.82-1.18).
†Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
‡Includes metastatic and non-metastatic breast cancer, with the exception of *in situ* breast cancer.

Women's Health Initiative Memory Study
The estrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45 percent were aged 65 to 69 years, 36 percent were aged 70 to 74 years, and 19 percent were 75 years of age and older) to evaluate the effects of daily conjugated estrogens (CE 0.625 mg) on the incidence of probable dementia (primary outcome) compared with placebo.
After an average follow-up of 5.2 years, 28 women in the estrogen alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen alone group was 1.49 (95 percent CI, 0.83-2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS**, **WARNINGS**, **Dementia**, and **PRECAUTIONS**, **Geriatric Use**.)
The estrogen plus progestin WHIMS substudy enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were aged 65 to 69 years, 35 percent were 70 to 74 years, and 18 percent were 75 years of age and older) to evaluate the effects of daily CE 0.625 mg plus medroxyprogesterone acetate (MPA 2.5 mg) on the incidence of probable dementia (primary outcome) compared with placebo.
After an average follow-up of 4 years, 40 women in the estrogen plus progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95 percent CI, 1.21-3.48) compared to placebo.
When data from the 2 populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is

unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNING**, **WARNINGS**, **Dementia**, and **PRECAUTIONS, Geriatric Use**.)

INDICATIONS AND USAGE
EstroGel is an estrogen indicated in the
1. Treatment of moderate to severe vasomotor symptoms due to menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

CONTRAINDICATIONS
EstroGel should not be used in women with any of the following conditions:
1. Undiagnosed abnormal genital bleeding

2. Known, suspected, or history of breast cancer

3. Known or suspected estrogen-dependent neoplasia

4. Active deep vein thrombosis, pulmonary embolism, or history of these conditions

5. Active or recent (within the past year) arterial thromboembolic disease (for example, stroke and myocardial infarction)

6. Known liver dysfunction or disease

7. Known hypersensitivity to any of the ingredients in EstroGel

8. Known or suspected pregnancy.

WARNINGS
See BOXED WARNINGS.

1. Cardiovascular Disorders
An increased risk of stroke and deep vein thrombosis (DVT) has been reported with estrogen alone therapy.
An increased risk of stroke, DVT, pulmonary embolism, and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogens with or without progestins should be discontinued immediately.
Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Stroke
In the Women's Health Initiative (WHI) estrogen alone substudy, a statistically significant increased risk of stroke was reported in women receiving daily conjugated estrogens (CE 0.625 mg) compared to placebo (45 versus 33 per 10,000 women-years). (See **CLINICAL STUDIES**.)

In the estrogen plus progestin substudy of WHI, a statistically significant increased risk of stroke was reported in women receiving daily CE 0.625 mg plus medroxyprogesterone acetate (MPA 2.5 mg) compared to placebo (31 versus 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted. (See **CLINICAL STUDIES**.)

b. Coronary heart disease
In the estrogen alone substudy of WHI, no overall effect on coronary heart disease (CHD) events (defined as non-fatal myocardial infarction [MI], silent MI, or CHD death) was reported in women receiving estrogen alone compared to placebo. (See **CLINICAL STUDIES**.)

In the substudy of WHI, no statistically significant increase of CHD events was reported in women receiving CE/MPA compared to women receiving placebo (39 versus 33 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5.

In postmenopausal women with documented heart disease (n= 2,763, average age 66.7 years), a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with daily CE 0.625 mg/ MPA 2.5 mg demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three

hundred twenty-one (2,321) women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

c. Venous thromboembolism (VTE)

In the estrogen alone substudy of WHI, the risk of VTE (DVT and pulmonary embolism [PE]), was reported to be increased for women receiving daily CE compared to women receiving placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years. (See **CLINICAL STUDIES.)**

In the estrogen plus progestin substudy of WHI, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE/MPA compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL STUDIES**.)

If feasible, estrogens should be discontinued at least 4 to 6 weeks before any surgery associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant Neoplasms

a. Endometrial cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen plus progestin therapy is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer in some studies. Observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen alone therapy after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of daily conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) (see **CLINICAL STUDIES**). In the estrogen alone substudy of WHI, after an average of 7.1 years of follow-up, daily CE 0.625 mg was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80, 95% nominal confidence interval [nCI], 0.62-1.04).

In the estrogen plus progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer in women who took daily CE/MPA. In this substudy, prior use of estrogen alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24 (95 percent nCI, 1.01-1.54), and the absolute risk was 41 versus 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo, respectively. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

c. Ovarian cancer

The estrogen plus progestin substudy of WHI reported that daily CE/MPA increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95 percent nCI, 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

3. Dementia

In the estrogen alone Women's Health Initiatives Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to daily conjugated estrogens (CE 0.625 mg) or placebo. In the estrogen plus progestin WHIMS, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to daily CE 0.625 mg plus medroxyprogesterone acetate (MPA 2.5 mg) or placebo.

In the estrogen alone substudy, after an average follow-up of 5.2 years, 28 women in the CE alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

In the estrogen plus progestin substudy, after an average follow-up of 4 years, 40 women in the CE/MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE/MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **PRECAUTIONS, Geriatric Use**.)

4. Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

A. General

1. Addition of a progestin when a woman has not had a hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (lowering HDL, raising LDL), and impairment of glucose tolerance.

2. Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertriglyceridemia

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. Consider discontinuation of treatment if pancreatitis or other complications develop.

4. Impaired liver function and past history of cholestatic jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued. Topically administered estrogen therapy avoids first-pass hepatic metabolism.

5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid-replacement therapy. These patients should have their thyroid function monitored in order to maintain an acceptable range.

6. Fluid retention

Estrogens may cause some degree of fluid retention. Patients who have conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

8. Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of estrogens. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

9. Exacerbation of other conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

10. Photosensitivity/Photoallergy

Increased sensitivity to direct exposure to the sun on areas of EstroGel application has not been evaluated.

11. Effect of sunscreen application

The effects of concomitant application of EstroGel and a sunscreen lotion have not been evaluated.

12. Alcohol-based gels are flammable.

Avoid fire, flame, or smoking until the gel has dried.

B. Patient Information

Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe EstroGel.

C. Laboratory Tests

Serum follicle stimulating hormone and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

D. Drug and Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and T_3 concentrations are unaltered. Patients on thyroid-replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (Corticosteroid-binding globulin [CBG], sex hormone-binding globulin [SHBG]), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

5. Impaired glucose tolerance.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

F. Pregnancy
EstroGel should not be used during pregnancy. (See **CONTRAINDICATIONS**.)
There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

G. Nursing Mothers
EstroGel should not be used during lactation. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogen have been identified in the milk of mothers receiving this drug.

H. Pediatric Use
EstroGel is not indicated for pediatric use and no clinical data have been collected in children.

I. Geriatric Use
There have not been sufficient numbers of geriatric patients involved in studies utilizing EstroGel to determine whether those over 65 years differ from younger subjects in their response to EstroGel.
In the estrogen alone substudy of the Women's Health Initiative (WHI) study, 46 percent (n=4,943) of subjects were 65 years and older, while 7.1 percent (n=767) of subjects were 75 years and older. There was a higher relative risk (daily CE 0.625 mg versus placebo) of stroke in women less than 75 years of age compared to women 75 years and older.
In the estrogen alone substudy of the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to receive daily conjugated estrogens (CE 0.625 mg) or placebo. After an average follow-up of 5.2 years, the relative risk (CE versus placebo) of probable dementia was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of developing probable dementia with estrogen alone was 37 versus 25 cases per 10,000 women-years compared with placebo.
Of the total number of subjects in the estrogen plus progestin substudy of WHI, 44 percent (n=7,320) were aged 65 years and older, while 6.6 percent (n=1,095) were 75 years and older. In women 75 years of age and older compared to women less than 75 years of age, there was a higher relative risk of non-fatal stroke and invasive breast cancer in the estrogen plus progestin group versus placebo. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed on the estrogen plus progestin group compared to placebo was 75 versus 24 per 10,000 women-years and 52 versus 12 per 10,000 women-years, respectively.
In the estrogen plus progestin substudy of WHIMS, a population of 4,532 postmenopausal women, aged 65 to 79 years, was randomized to receive daily CE 0.625 mg /MPA 2.5 mg or placebo. In the estrogen plus progestin group, after an average follow-up of 4 years, the relative risk (CE/MPA versus placebo) of probable dementia was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of developing probable dementia with CE/MPA was 45 versus 22 cases per 10,000 women-years compared with placebo.
Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 years for the CE alone group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 years in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer's disease.
When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS, Dementia**.)

ADVERSE EVENTS
See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS.**
Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
EstroGel 1.25 g was studied in 2 well-controlled 12-week clinical trials. Incidence of adverse events ≥5 percent for 1.25 g EstroGel and placebo is given below in Table 4.
TABLE 4 Incidence of Treatment-emergent Signs and Symptoms ≥5 Percent By COSTART Body System and by Descending Frequency of Occurrence in the EstroGel Treatment Group for the Intent-to-Treat Safety Population in 2 Well-controlled Clinical Studies (Expressed as Percent of Treatment Group)

Body System/Treatment-emergent Signs and Symptoms	EstroGel 1.25 g day (n=168)	Placebo (n=73)
BODY AS A WHOLE		
Headache	20.2	17.8
Infection*	17.3	6.8
Pain†	7.1	11.0
Abdominal pain	7.7	1.4
Back pain	4.8	4.1
Flu syndrome	5.4	1.4

Asthenia	4.8	4.1
CARDIOVASCULAR SYSTEM		
Palpitations	0.6	1.4
DIGESTIVE SYSTEM		
Nausea	6.0	4.1
Flatulence	6.5	5.5
Diarrhea	4.2	0.0
METABOLIC and NUTRITIONAL SYSTEMS		
Weight gain	2.4	0.0
NERVOUS SYSTEM		
Nervousness	2.4	1.4
Depression	3.0	2.7
Anxiety	1.8	0.0
RESPIRATORY SYSTEM		
Sinusitis	3.6	1.4
Rhinitis	2.4	6.8
SKIN AND APPENDAGES		
Rash‡	7.1	5.5
Pruritus‡	4.8	2.7
Application-site reaction	0.6	0.0
UROGENITAL		
Breast pain	12.5	9.6
Metrorrhagia	3.0	0.0
Endometrial disorder§	1.8	1.4
Vaginitis	8.9	4.1
Pap smear suspicious¶	5.4	2.7
Vaginal hemorrhage	1.2	0.0

*****Infection: upper respiratory infection, common cold, eye infection.

†Pain: generalized and extremity aches/pains, cramps.

‡Rash and pruritus: more than half of the EstroGel-treated patients who had pruritus reported itching at a body site other than the arms or reported generalized itching or itching skin. Similarly, most of the EstroGel-treated patients with rash had rash on 1 or more areas of the body in addition to the arms.

§Endometrial disorder: proliferative endometrium, benign endometrial disorders.

¶Pap smear suspicious: atypical squamous cells of undetermined significance, inflammatory changes, epithelial cell abnormality.

The following additional adverse events have been reported with estrogen and/or progestin therapy.

1. **Genitourinary system:** abnormal uterine bleeding/spotting; dysmenorrhea/pelvic pain; increase in size of uterine leiomyomata; vaginitis including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer

2. **Breasts:** tenderness; enlargement; pain; nipple discharge; galactorrhea; fibrocystic breast changes; breast cancer

3. **Cardiovascular:** deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure

4. **Gastrointestinal:** nausea; vomiting, abdominal cramps; bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas

5. **Skin:** chloasma or melasma, that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus; rash

6. **Eyes:** retinal vascular thrombosis; intolerance to contact lenses

7. **Central nervous system:** headache; migraine; dizziness; mental depression; exacerbation of chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy; dementia

8. **Miscellaneous:** increase or decrease in weight; glucose intolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; urticaria; angioedema; anaphylactoid/anaphylactic reactions; hypocalcemia (preexisting condition); exacerbation of asthma; increased triglycerides

OVERDOSAGE

Overdosage of estrogen may cause nausea and vomiting, breast tenderness, abdominal pain, drowsiness/fatigue and withdrawal bleeding may occur in females. Treatment of overdose consists of discontinuation of EstroGel together with institution of appropriate symptomatic care.

DOSAGE AND ADMINISTRATION

EstroGel 1.25 g is the single approved dose for the treatment of moderate to severe vasomotor symptoms and for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. The lowest effective dose of EstroGel for these indications has not been determined. When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

When estrogen is prescribed for a postmenopausal woman with a uterus, generally, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (for example at 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

EstroGel is a clear, colorless, hydroalcoholic 0.06% estradiol gel supplied in a non-aerosol, metered-dose pump. The pump consists of an LDPE inner liner encased in rigid plastic with a resealable polypropylene cap. Three pump sizes are available, a 93-gram, a 50-gram, and a 25-gram. Each individually packaged 93-gram pump contains 93 grams of gel and is capable of delivering 64 metered 1.25-g doses. Each individually packaged 50-gram pump contains 50 grams of gel and is capable of delivering 32 metered 1.25-g doses. Each individually packaged 25-gram pump contains 25 grams of gel and is capable of delivering 14 metered 1.25-g doses.

NDC: 0051-1028-58……..... (93-gram pump)
NDC: 17139-617-40……..... (50-gram pump)
NDC: 17139-617-20……... (25-gram sample pump)
NDC: 0051-1028-20……..... (25-gram sample pump)

Keep out of reach of children.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)
[See USP Controlled Room Temperature].

Manufactured for:
ASCEND Therapeutics, Inc.
Herndon, VA 20170
By Laboratoires Besins International
Montrouge, France
5000718
E01306

Utilizes EHG™ Technology

PATIENT INFORMATION

(Updated 2008)

EstroGel®

(estradiol gel)

Read this PATIENT INFORMATION before you start using EstroGel, and read the patient information each time you refill your EstroGel prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms and their treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT EstroGel (AN ESTROGEN HORMONE)?

• Estrogens increase the chance of getting cancer of the uterus.

Report any unusual vaginal bleeding right away while you are using EstroGel. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find the cause.

• Do not use estrogens with or without progestins to prevent heart disease, heart attacks, strokes or dementia.

Using estrogens, with or without progestins, may increase your chance of getting heart attacks, strokes, breast cancer, and blood clots.

Using estrogens, with or without progestins, may increase your risk of dementia, based on a study of women age 65 or older.

You and your healthcare provider should talk regularly about whether you still need treatment with EstroGel.

What is EstroGel?

EstroGel is a clear, colorless gel medicine that contains estradiol (an estrogen hormone) which is absorbed through the skin into the bloodstream.

How is EstroGel used?

EstroGel is used after menopause to:

• Reduce moderate to severe hot flashes

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

When the estrogen levels begin dropping, some women have very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogen treatment. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with EstroGel.

• Treat moderate to severe dryness, itching, and burning in or around your vagina

You and your healthcare provider should talk regularly about whether you still need treatment with EstroGel to control these problems. If you use EstroGel only to treat your dryness, itching, and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

Who should not use EstroGel?

Do not start using EstroGel if you:

- **Have unusual vaginal bleeding**

- **Currently have or have had certain cancers**
  Estrogens may increase the chance of getting certain types of cancer, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use EstroGel.

- **Had a stroke or heart attack in the past year**

- **Currently have or have had blood clots**

- **Currently have or have had liver problems**

- **Are allergic to EstroGel or any of its ingredients**
  See the list of ingredients in EstroGel at the end of this leaflet.

- **Think you may be pregnant**

Tell your healthcare provider:

- **If you are breastfeeding**
  The hormone in EstroGel can pass into your breast milk.

- **About all of your medical problems**
  Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, or problems with your heart, liver, thyroid, kidneys, or high calcium levels in your blood.

- **About all the medicines you take**
  This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how EstroGel works. EstroGel may also affect how your other medicines work.

- **If you are going to have surgery or will be on bedrest**
  You may need to stop taking estrogens.

How should I use EstroGel?
EstroGel is available in a metered-dose pump that delivers a measured amount of estradiol to the skin each time the pump is depressed.
It is important that you read and follow these directions on how to use the EstroGel pump properly.

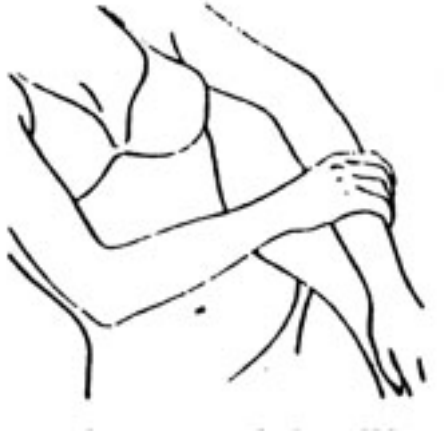
1. **Before using the pump for the first time, it must be primed**. Remove the large pump cover, and fully depress the pump twice for the 93-gram pump or 3 times for the 50-gram pump and the 25-gram pump. Discard the unused gel by thoroughly rinsing down the sink or placing it in the household trash. **After priming, the pump is ready to use**, and 1 complete pump depression will dispense the same amount of EstroGel each time.

2. **Apply EstroGel at the same time each day.** You should apply your daily dose of gel to clean, dry, unbroken skin. If you take a bath or shower or use a sauna, apply your EstroGel dose after your bath, shower, or sauna. If you go swimming, try to leave as much time as possible between applying your EstroGel dose and going swimming.

3. **Be sure your skin is completely dry before applying EstroGel.**

4. To apply the dose, collect the gel into the palm of your hand by pressing the pump firmly and fully once, as illustrated.

5. Apply the gel to the skin of one arm using your hand. Spread the gel as thinly as possible over the entire area on the inside and outside of your arm from wrist to shoulder, as illustrated.



6. Always place the small protective cap back on the tip of the pump and the large pump cover over the top of the pump after each use.

7. **Wash your hands with soap and water after applying the gel to reduce the chance that the medicine will spread from your hands to other people.**

8. It is not necessary to massage or rub in EstroGel. Simply allow the gel to dry for up to 5 minutes before dressing.

9. Alcohol-based gels are flammable. Avoid fire, flame or smoking until the gel has dried.

10. Once dry, EstroGel is odorless.

11. **Never apply EstroGel directly to the breast.** Do not allow others to apply the gel for you.

12. The EstroGel 93-gram pump contains enough medicine to allow for initial priming of the pump twice and delivery of 64 daily doses. After you have initially primed the pump twice and dispensed 64 doses, you will need to discard the pump.

13. The EstroGel 50-gram pump contains enough medicine to allow for initial priming of the pump 3 times and delivery of 32 daily doses. After you have initially primed the pump 3 times and dispensed 32 doses, you will need to discard the pump.

14. The EstroGel 25-gram pump contains enough medicine to allow for initial priming of the pump 3 times and delivery of 14 daily doses. After you have initially primed the pump 3 times and dispensed 14 doses, you will need to discard the pump.

What should I do if someone else is exposed to EstroGel?
If someone else is exposed to EstroGel by direct contact with the gel, that person should wash the area of contact with soap and water as soon as possible. The longer the gel is in contact with the skin before washing, the greater the chance that the other person will absorb some of the estrogen hormone. This is especially important for men and children.
What should I do if I get EstroGel in my eyes?
If you get EstroGel in your eyes, rinse your eyes right away with warm, clean water to flush out any gel. Seek medical attention if needed.
What should I do if I miss a dose?
If you miss a dose, do not double the dose on the next day to catch up. If your next dose is less than 12 hours away, it is best just to wait and apply your normal dose the next day. If it is more than 12 hours until the next dose, apply the dose you missed, and resume your normal dosing the next day.
What should I avoid while using EstroGel?
It is important that you do not spread the medicine to others, especially men and children. Be sure to wash your hands after applying EstroGel. Do not allow others to make contact with the area of skin where you applied the gel for at least 1 hour after application. Alcohol-based gels are flammable. Avoid fire, flame or smoking until the gel has dried.
What are the possible side effects of estrogens?
Side effects are grouped by how serious they are and how often they happen when you are treated.
Serious but less common side effects include:
• Breast cancer

• Cancer of the uterus

• Stroke

- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer
- High blood pressure
- Liver problems
- High blood sugar
- Enlargement of benign tumors of the uterus (“fibroids”)

Some of the warning signs of these serious side effects include:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting
- Yellowing of the skin, eyes or nail beds

Call your healthcare provider right away if you have any of these warning signs, or any other unusual symptoms that concern you.

Less serious but common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

These are not all of the possible adverse events of EstroGel. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of having an adverse event with EstroGel?

- Talk with your healthcare provider regularly about whether you should continue using EstroGel.

- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin (a different prescribed hormone) is right for you. The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the uterus.

- See your healthcare provider right away if you get vaginal bleeding while using EstroGel.

- Have a pelvic exam, breast exam and mammogram (breast x-ray) every year unless your healthcare provider tells you otherwise. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.

- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances of getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart disease.

General information about the safe and effective use of EstroGel

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use EstroGel for conditions for which it was not prescribed. Do not give EstroGel to other people, even if they have the same symptoms you have. It may harm them.

Keep EstroGel out of the reach of children.

This leaflet provides a summary of the most important information about EstroGel. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about EstroGel that is written for health professionals. You can get more information by calling the toll-free number, 1-877-204-1013.

What are the ingredients in EstroGel?

EstroGel contains estradiol (an estrogen hormone), purified water, alcohol, triethanolamine, and carbomer 934P.

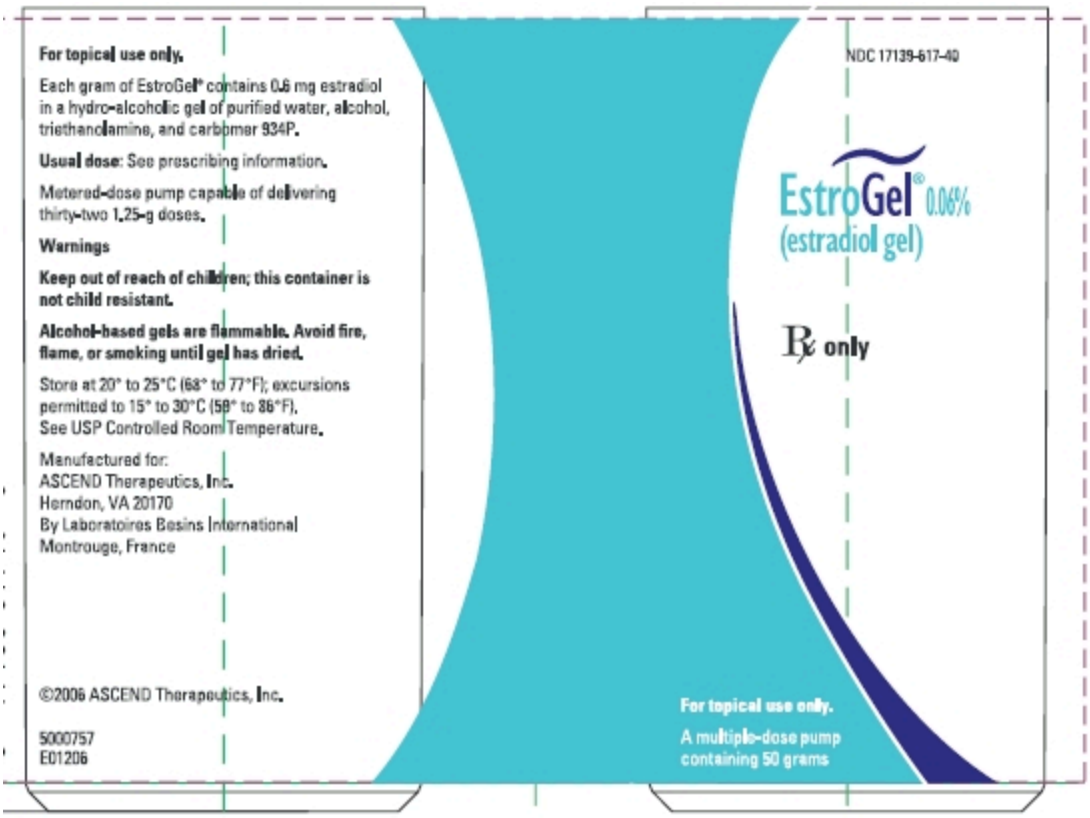
EstroGel should be stored with the cap on securely. Do not freeze. The gel should not be used after the date printed on the end of the metered-dose pump after the term “Exp.” (expiration date).

Manufactured for:

ASCEND Therapeutics, Inc.
Herndon, VA 20170
By Laboratoires Besins International
Montrouge, France
5000718
E01306

Utilizes EHG^{TM} Technology

PRINCIPAL DISPLAY PANEL - ESTROGEL 50G CANISTER



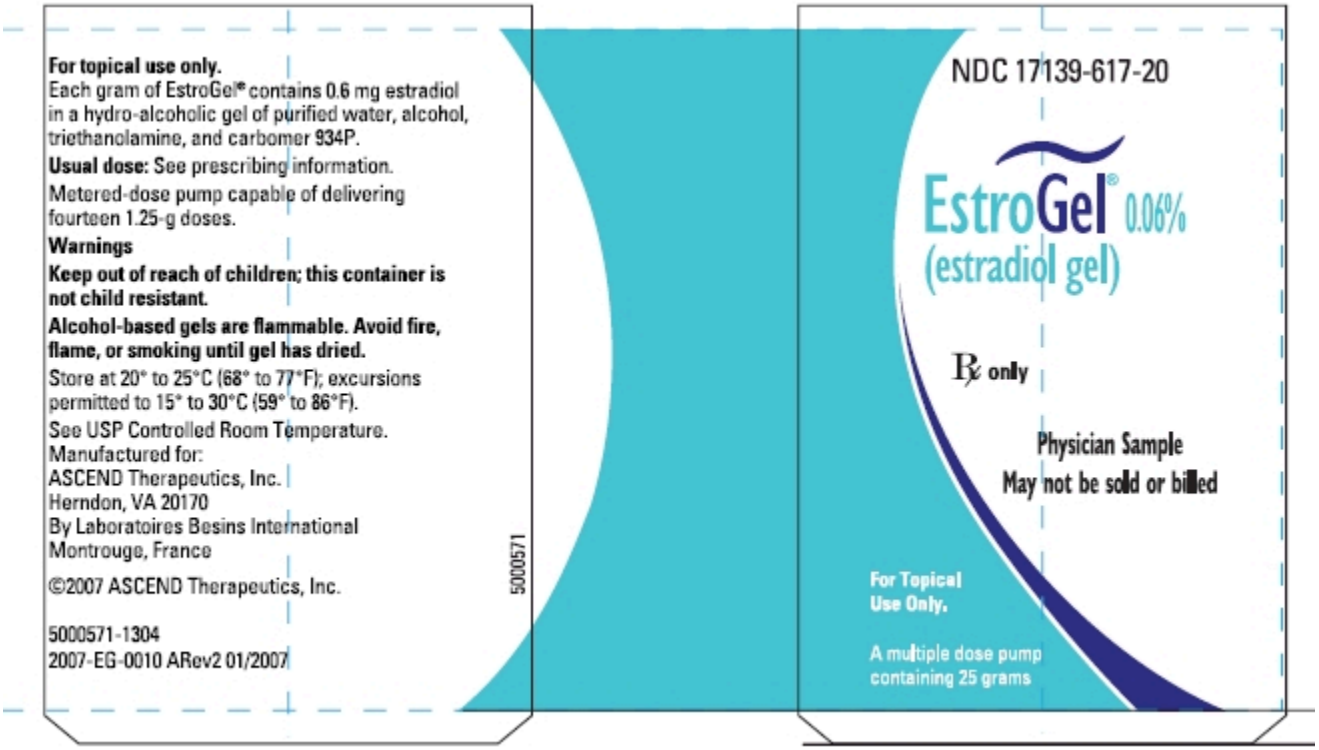
NDC 17139-617-40
EstroGel® 0.06%
(estradiol gel)
Rx only
For topical use only.
A multiple-dose pump
containing 50 grams

PRINCIPAL DISPLAY PANEL - ESTROGEL 50G CARTON

NDC 17139-617-40

EstroGel® 0.06%
(estradiol gel)
Rx only
For topical use only.
A multiple-dose pump
containing 50 grams

PRINCIPAL DISPLAY PANEL - ESTROGEL 25G SAMPLE CANISTER



NDC 17139-617-20
EstroGel® 0.06%
(estradiol gel)
Rx only
Physician Sample
May not be sold or billed
For Topical Use Only.
A multiple dose pump
containing 25 grams

PRINCIPAL DISPLAY PANEL - ESTROGEL 25G SAMPLE CARTON

NDC 17139-617-20

EstroGel® 0.06%
(estradiol gel)
Rx only
Physician Sample
May not be sold or billed
For topical use only.
A multiple-dose pump
containing 25 grams

Revised: 01/2010

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